Prior art

Hyaluronic acid is an acid mucopolysaccharide which constitutes more than 50% of the basic substance of the dermis. Administration of exogenous hyaluronic acid determines an antiphlogistic and stimulating action on the granulation tissue, which accelerates cicatrization and re-epithelialization of lesions.

Pharmaceutical compositions comprising hyaluronic acid are known. For example, USA patent 4,736,024 describes compositions for topical application comprising hyaluronic acid and pharmacologically active substances, consisting for example of antibiotics such as erythromycin, gentamicin, neomycin etc.

European patent 0138572 describes pharmaceutical compositions comprising hyaluronic acid sodium or potassium salt for treating wounds and for use in the ophthalmic field.

The patent WO 84/04453 describes compositions for oral and dental treatment.

However, the problem of preparing compositions comprising hyaluronic acid and disinfectant substances has as yet not been solved. In this respect, various difficulties are encountered such as the poor compatibility between many disinfectant substances and hyaluronic acid, poor biocompatibility with the skin in prolonged topical use, etc.

For example, quaternary ammonium salts, guanidine and biguanidine derivatives and acridine derivatives precipitate the hyaluronic acid by complexing; mercury and phenol derivatives develop high toxicity and cause damage determined by their long retention time on the dermis; benzoic acid derivatives in association with antimycotics give rise to frequent allergic manifestations; iodine-based derivatives excessively colour the preparations and give rise to formulations of poor physico-chemical stability.

Summary of the invention

We have now unexpectedly found that compositions comprising hyaluronic acid and disinfectant substances can be prepared having compatibility between the components and biocompatibility with the cutis, if the disinfectants are chosen from the group consisting of cresol derivatives, hexetidine, sulfadiazine silver and sulfadiazine zinc salt.

Said compositions can be used with excellent results in the topical treatment of infected sores.

Detailed description of the invention

The characteristics and advantages of the pharmaceutical compositions comprising hyaluronic acid sodium salt and disinfectant substances according to the present invention will be apparent in the course of the following detailed description.

In addition to the hyaluronic acid sodium salt and disinfectant substances the compositions also comprise pharmacologically acceptable excipients and diluents suitable for obtaining the desired pharmaceutical forms.

The disinfectant substances are chosen from the group consisting of cresol derivatives, hexetidine, sulfadiazine silver and sulfadiazine zinc salt. The preferred cresol derivatives are chloroxylenol and dichloroxylenol.

The compositions can be prepared in various pharmaceutical forms suitable for use in topical treatment, such as oil-in-water emulsions, water-in-oil emulsions, hydrogels, pastes, ointments, lotions and powders for sprinkling.

The excipients used include for example hydroxypropylmethylcellulose, sorbitol, glycerin, polyoxyethylenated glycolyzed glycerides, polyethyleneglycol stearate, stearic acid, oleic acid decyl ester, caprylic and caproic acid esters, ethoxylated glycerides of palmitic and lauric acids, polymerized polyvinyl alcohol, self-emulsifying wax and non-denatured collagen.

The hyaluronic acid sodium salt content of the composition is between 0.1 and 0.5% by weight and the disinfectant substance content is between 0.1 and 2% by weight.

The composition pH depends on the pH of maximum activity of the disinfectant substance used but in all cases is between 4 and 7. The compositions in water-in-oil emulsion form have an HLB of 1-5 and the compositions in oil-in-water emulsion form have an HLB of 8-21.

Of the disinfectant substances suitable for use in preparing the compositions of the present invention, the preferred substance is sulfadiazine silver.

This substance is in fact the choice antimicrobic for disinfecting sores, burns, ulcerations etc. It is insoluble in water, it dissociates gradually in the organic liquids of the damaged surfaces and subsequently binds to the cellular walls of the infecting micro-organisms or of the epithelial cells.

This results in a slow and continuous antiseptic effect and prevents absorption of two ions (metal and

organic).

In this respect, sulfadiazine silver does not produce argyric phenomena, and in addition the sulphamide part is poorly absorbed cutaneously, with the result that urinary elimination in 24 hours is of the order of 50 mg on average, this being a value considered far below the threshold for inducing renal damage.

The activity of sulfadiazine silver is not antagonized by p-aminobenzoic acid and in particular does not inhibit carbonic anhydrase, so preventing systemic acidosis.

Finally, it has a wide range of action, in particular against gram-negative micro-organisms, including Pseudomonas aeruginosa, Enterobacter cloacae and klebsiella, and against Staphylococcus aureus.

The association of hyaluronic acid and sulfadiazine silver is chemically and biologically compatible, and develops a synergic effect which results in rapid re-epithelialization of the damaged tissue in an aseptic environment.

The antibacterial activity of the association of hyaluronic acid sodium salt with sulfadiazine silver in a 1:5 ratio (as in Examples 4 and 5) was evaluated in vitro on certain bacterial strains and fungi, in comparison with the two components taken separately.

Although hyaluronic acid proved, as predictable, totally free of antibacterial effect, its association with the sulfadiazine silver led to an unexpected potentiation of the sulfadiazine activity.

This potentiation is of considerable interest from the applicative clinical-therapeutic aspect.

Table 1 below shows the MIC (minimum inhibiting concentration) values of sulfadiazine silver both alone (A) and in its association with hyaluronic acid sodium salt in the described ratio (B). The values are expressed as µg/ml of sulfadiazine silver.

TABLE 1

STRAIN		MIC (µg/ml)	
		A	B
GRAM+	Staphylococcus Aureus ATCC 6538	62.5	15.26
GRAM-	Pseudomonas Aeruginosa ATCC 9027	62.5	31.25
FUNGUS	Candida Albicans ATCC 10231	31.25	15.62

Some examples are given hereinafter of topical pharmaceutical forms of the compositions according to the present invention. These examples are provided by way of illustration without limiting the scope of the invention.

EXAMPLE 1:

Composition in the form of an oil-in-water emulsion:	
Hyaluronic acid sodium salt	0.1 - 0.5% by weight
Hexetidine	0.05 - 0.5% by weight
Glycolyzed polyoxyethylenated glycerides	1 - 5 % by weight
Polyethyleneglycol stearate and stearic acid	2 - 4 % by weight
Sorbitol	1 - 2 % by weight
Distilled water to make up to	100 % by weight

The emulsion has an HLB of 11 and a pH of 6.5-7. The disinfectant is dissolved in the lipid phase.

EXAMPLE 2:

Composition in the form of a translucent hydrogel:

Hyaluronic acid sodium salt		0.1 - 0.5% by weight
Hexetidine		0.1 - 0.3% by weight
Polymerized polyvinyl alcohol		1 - 5 % by weight
NaOH solution	to make up to pH 7	
Sorbitol		2 - 4 % by weight
Distilled water	to make up to	100 % by weight

The disinfectant is present in microdispersed form.

EXAMPLE 3:

Composition in the form of a water-in-oil emulsion:	
Hyaluronic acid sodium salt	0.1 - 0.5% by weight
Chlorocresol	0.1 - 1.0% by weight
Oleic acid decyl ester	15 - 20 % by weight
Caprylic and caproic acid esters	5 - 10 % by weight
Ethoxylated glycerides of palmitic and lauric acids	20 - 30 % by weight
Distilled water to make up to	100 % by weight

The emulsion has an HLB of 4. The disinfectant is dissolved in the lipid phase.

EXAMPLE 4:

Composition in the form of an oil-in-water emulsion:	
Hyaluronic acid sodium salt	0.1 - 0.5% by weight
Sulfadiazine silver	1 - 2 % by weight
Glycerin	1 - 2 % by weight
Sorbitol	1 - 3 % by weight
Polyethyleneglycol stearate	8 - 12 % by weight
Oleic acid decyl ester	4 - 6 % by weight
Self-emulsifying cream	1.5 - 3 % by weight
Distilled water to make up to	100 % by weight

The emulsion has an HLB of 12 and a pH of 6-7. The disinfectant is micro-dispersed in the aqueous phase.

EXAMPLE 5:

Composition in the form of a translucent hydrogel:	
Hyaluronic acid sodium salt	0.1 - 0.5% by weight
Sulfadiazine silver	1 - 2 % by weight
Glycerin	2 - 7 % by weight
Non-denatured collagen	1 - 4 % by weight
Sorbitol	1 - 2 % by weight
Distilled water to make up to	100 % by weight

The hydrogel has a pH of 6-7. The disinfectant is present in micro-dispersed form.

EXAMPLE 6:

Composition in the form of an oil-in-water emulsion:	
Hyaluronic acid sodium salt	0.1 - 0.5% by weight
Sulfadiazine zinc salt	1 - 2 % by weight
Glycerin	1 - 2 % by weight
Sorbitol	1 - 3 % by weight
Polyethyleneglycol stearate	8 - 12 % by weight
Oleic acid decyl ester	4 - 6 % by weight
Self-emulsifying cream	1.5 - 3 % by weight
Distilled water to make up to	100 % by weight

The emulsion has an HLB of 12 and a pH of 6-7. The disinfectant is micro-dispersed in the aqueous phase.

Claims

1. Pharmaceutical compositions for topical use comprising hyaluronic acid sodium salt and disinfectant substances chosen from the group consisting of cresol derivatives, hexetidine, sulfadiazine silver and sulfadiazine zinc salt.

2. Compositions as claimed in claim 1, characterised in that said cresol derivatives are chloroxylenol and dichloroxylenol.

3. Compositions as claimed in claim 1, characterised by comprising as excipients and diluents hydroxypropylmethyl-cellulose, sorbitol, glycerin, polyoxyethylenated glycolyzed glycerides, polyethyleneglycol stearate, stearic acid, oleic acid decyl ester, caprylic and caproic acid esters, ethoxylated glycerides of palmitic and lauric acids, polymerized polyvinyl alcohol, self-emulsifying wax and non-denatured collagen.

4. Compositions as claimed in claim 1, characterised by being prepared in the form of oil-in-water emulsions, water-in-oil emulsions, hydrogels, pastes, ointments, lotions and powders for sprinkling.

5. Compositions as claimed in claim 1, characterised by a hyaluronic acid sodium salt content of between 0.1 and 0.5% by weight and a disinfectant substance content of between 0.1 and 2.0% by weight.

6. Compositions as claimed in claim 1, characterised by a pH of between 4 and 7.

7. Compositions as claimed in claim 1, characterised in that when prepared in the form of a water-in-oil emulsion they have an HLB of between 1 and 5.

8. Compositions as claimed in claim 1, characterised in that when prepared in the form of an oil-in-water emulsion they have an HLB of between 6 and 21.

9. The use of pharmaceutical compositions comprising hyaluronic acid sodium salt and disinfectant substances chosen from the group consisting of cresol derivatives, hexetidine, sulfadiazine silver and sulfadiazine zinc salt for the topical treatment of sores, ulcerations and burns.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 11 5360

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X,D	US-A-4 736 024 (FIDIA, S.P.A.) * claims 1,7 * ---	1	A 61 K 31/73 // (A 61 K 31/73 A 61 K 31:635 A 61 K 31:05 A 61 K 31:505)
A	GB-A-1 240 545 (RES. CORP.) * claims * ---	1-9	
A	RIV. ITAL. PLAST. (ITALY), vol. 19, no. 4, 1987, PADOVA, pages 635-644; SILIPRANDI et al.: "Hyaluronic acid effects on deep burns healing" * Summary * -----	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	13-01-1992	LEHERTE C.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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